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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,868	10/31/2003	Christopher A. Gabel	50323/009003	2027

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EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,868	GABEL ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/31/03 (filing date)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3 are pending and under current examination.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 3 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 6,677,501. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to cells, particularly ES cells, that have the same disruption. The instant claims are directed to any ES cell, and then limit the cell to a murine ES cell. The '501 claims are directed to a mouse ES cell, which is encompassed by a murine ES cell. Thus, a mouse ES cell would be obvious over a murine or any species ES cell.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cultured mouse ES cell, wherein the genome of said ES cell comprises a homozygous disruption of the P_{2x7} receptor, wherein the cell lacks functional endogenous P_{2x7}, and wherein the cell exhibits a phenotype of reduced ATP-stimulated post-translation processing of interleukin-1α (IL-1α), IL-1β, IL-18 or reduced ATP-stimulated IL-6 production, or reduced ATP-stimulated intracellular accumulation of macromolecules, and a macrophage isolated from a transgenic mouse whose genome comprises a disruption of the P_{2x7} receptor, wherein the mouse lacks functional endogenous P_{2x7} and the macrophage exhibits the above-recited phenotypes, does not reasonably provide enablement for the breadth of the claims, drawn to an ES cell from any species with a disruption in the P_{2x7} receptor, the production and isolation of a macrophage by *in vitro* differentiation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The invention is directed to cultured ES cells, comprising a homozygous disruption of the P_{2x7} receptor, wherein a cultured macrophage differentiated from said ES cell exhibits a phenotype of reduced ATP-stimulated post-translation processing of interleukin-1α (IL-1α), IL-1β, IL-18 or reduced ATP-stimulated IL-6 production, or reduced ATP-stimulated intracellular accumulation of macromolecules.

Breadth of the claims. The claims are broadly drawn to an ES cell from any species, wherein specific embodiments limit the species of ES cell to human (claim 2) or murine (claim 3).

Guidance of the Specification/The Existence of Working Examples. The specification teaches that methods of producing non-human genetically-modified mammals and animal cells containing a disrupted $P_{2x7}R$ gene that prevents or reduces endogenous $P_{2x7}R$ function (see p. 4, lines 34-36). The specification teaches that the genetically modified non-human animals of the invention can be made by homologous recombination (see p. 11-12, bridging paragraph). In particular, the specification teaches the generation of $P_{2x7}R$ knockout mice (see Example 1). The specification teaches that a targeting vector was constructed containing a neomycin resistance gene direction after the Arg505 codon deleting Cys^{506}-Pro^{532} in the carboxy region of the $P_{2x7}R$ gene (see p. 33, lines 32-35). The specification teaches that 129/Ola ES cells were grown, transformed and screened and homologous recombination events between the vector and ES cells, as well as the genotyping of the mice, were detected (see p. 34). Chimeric mice derived from targeted ES cells were then mated with B6D2 mice to produce heterozygous animals. These heterozygous animals were then bred to produce homozygous mutant (-/-) mice (see p. 34, lines 21-26). The specification teaches that peritoneal macrophages were isolated from the $P_{2x7}R$ -/- mice and wild-type mice. These macrophages were compared to examine the ability of $P_{2x7}R$ to facilitate the translocation of organic the presence and absence of ATP, macrophages from the $P_{2x7}R$ -/- mice

demonstrated a low fluorescence when compared to wild-type mice (see Figure 4A). Wild type and $P_{2x7}R$ -/- peritoneal macrophages were then analyzed for stimulus-coupled IL-1β posttranslational processing, it was found that the $P_{2x7}R$ -/- macrophages were not able to release or produce mature IL-1β in response to ATP challenge (see page 39). The specification teaches the characterization of *in vivo* cytokine production capabilities. Wild-type and $P_{2x7}R$ -/- mice were primed with an injection of either LPS or PBS, and two hours later, injected with either ATP or PBS and incubated for an additional 4 hours. The peritoneal lavages were then collected during the course of the experiment and analyzed for IL-6 production (see p. 40) and it was found that the $P_{2x7}R$ -/- mice generated lover levels of IL-6 than their wild-type counterparts.

State of the Art/Predictability of the Art. The claims require 1) cultured ES cells from any species, 2) a targeted homozygous disruption of the P_{2x7} receptor of said ES cells, 3) the differentiation of said ES cell to a macrophage. The specification only teaches cultured mouse ES cells containing the specific P_{2x7} disruption, production of knockout mice using the cultured mouse ES cells, and the analysis of mouse macrophages from the knockout mouse. The specification provides no teachings or guidance with regard to the breadth of ES cells encompassed in the claims, for any species, nor does the specification provide specific guidance as to how to isolate these cells, perform a targeted, homozygous disruption of the P_{2x7} receptor gene, and then differentiation of the ES cell to a macrophage.

The specification contemplates isolating ES cells from genetically modified non-human mammals (p. 11, lines 23-25). The specification specifically contemplates using ES cells, as instantly-claimed, in order to produce transgenic animals. However, the state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species (see Moreadith *et al.*, **J. Mol. Med.**, 1997, p. 214, S*ummary,* cited on

Applicants' IDS, filed 2/2/04). Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Moreadith *et al.* supports this observation as they discuss the historical perspective of mouse ES cells as follows:

"The stage was set-one could grow normal, diploid ES cells in culture for multiple passages without loss of the ability to contribute to normal development. Furthermore, the cells contributed to the development of gametes at a high frequency (germline competence) and the haploid genomes of these cells were transmitted to the next generation. Thus, the introduction of mutations in these cells offered the possibility of producing mice with a predetermined genotype."

Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of <u>any</u> species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal. In addition, prior to the time of filing, Mullins *et al.* (**Journal of Clinical Investigation**, 1996, cited on Applicants' IDS, filed 2/2/04) report that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page 1558, column 2, first paragraph). As the claims are drawn to methods involving the manipulation of animal embryonic stem (ES), and particularly since the subject matter of the specification and the claimed invention encompasses the use of such cells for the generation of a transgenic animal, the state of the art supports that only **<u>mouse ES cells</u>** were available at the time of filing. Furthermore, it is noted that claim 3, which is directed to a "murine" ES cell is non-enabling, because it encompasses various species of animal, including rats, from which ES cells that contribute predictably to the germline, have not been isolated.

Furthermore, the phenotype of any cell that is gene-targeted, as instantly claimed, is unpredictable. One of skill in the art could not readily rely upon the

state of the art with regard to predicting the phenotype of a particular disruption. Even in the production of transgenic mice, this is found to be the case, and thus, specific guidance must be provided in order to enable the instant invention. The mere capability to perform gene transfer in a mouse ES is not enabling because a desired phenotype cannot be predictably achieved by simply introducing transgene constructs of the types recited in the claims. For example, Leonard [**Immunological Reviews**, (148): 98-113 (1995)] disclose mice with a disruption in the g_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (Abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths [**Microscopy Research and Technique**, **41**:344-358 (1998)] taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph). Thus, at the time of filing, the resulting phenotype of a knockout a particular gene was considered unpredictable, thus, one of skill would not know how to predict the resulting phenotype.

The claims require the specific targeting of the P_{2x7} receptor gene. The specification contemplates accomplishing this targeting by homologous recombination. Although one of skill in the art would be knowledgeable with regard to homologous recombination in mouse ES cells, one of skill in the art could not apply the same techniques used in mouse ES cells to, for example, human ES cells, at the time of filing, without undue experimentation. Zwaka *et al.* (**Nature**, 21:319-321, March 2003) is post-filing art that states, "Significant differences between mouse and human ES cells have hampered the development of homologous recombination in human ES cells. High, stable transfection efficiencies in human ES cells have been difficult to achieve, and, in particular, electroporation protocols established for mouse ES cells work poorly in human ES cells. Also, in contrast to

their murine counterparts, human ES cells cannot be cloned efficiently from single cells, making it difficult to screen for rare recombination events." See Abstract. Significantly, Zwaka *et al.* state that they were required to re-evaluate the mouse protocol used to electroporate human ES cells, because the existing protocol only yielded about 1% of human ES cells that were capable of survival and forming colonies (p. 319, 2nd col., 1st full ¶). Thus, one of skill in the art, given the state and predictability of the art of homologous recombination in ES cells, at the time of filing, could not produce the breadth of ES cells, as instantly claimed, without undue experimentation.

The working examples in the specification are not analogous to what is instantly claimed – *in vitro* differentiation of ES cells to a macrophage. The working examples are directed to isolation of macrophages from a mouse using a mouse ES cell with a P_{2x7} receptor disruption. In general, the state of the art of directed differentiation of ES cells is unpredictable. Verfaillie *et al.* [**Hematology** (Am Soc Hematol Educ Program). 2002;:369-91] who review the state of the art of stem cells at the time of filing, teach, that, with regard to the directed differentiation of ES cells, "Many proposed applications of human ES cells are predicated on the assumption that it will be possible to obtain pure populations of differentiated cells from the ES cultures. It might be envisioned that in order to achieve this one would treat ES cells with inducing agents that would convert them with high efficiency to a cell type of interest. In practice, that has not proven possible [even] with the mouse system." See p. 278, 2nd column, Differentiation in vitro. They further teach that a range of approaches have been attempted to produce a highly homogenous population of differentiated cells from ES cells, for example, relying upon the spontaneous differentiation of the ES cells to embryoid bodies. However, embryoid bodies contain a range of differentiated cells, which is a recognized limitation of directed differentiation of ES cells. Verfaillie teach that the ES cells can be treated with particular agents/factors that can drive differentiation

along a specific lineage (see p. 379, 1st column, 1st full ¶. However, it is clear that directed differentiation of ES cells to generate a particular cell type of interest is unpredictable. Thus, specific guidance must be provided to enable the claimed invention.

The Amount of Experimentation Necessary. Accordingly, in view of the lack of specific teachings or guidance provided by the specification with regard to cultured ES cells, from species other than mouse, the production and isolation of cultured macrophages by *in vitro* differentiation of ES cells, the unpredictable state of the art with regard to isolation of ES cells from species other than mice, as well as the resultant phenotype of a cell upon disruption of a particular gene, and the unpredictable state of the art with regard to specific gene targeting, such that one of skill in the art could not readily and predictably apply techniques used in mouse ES cells to, for example, human ES cells, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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